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Case Report

Title

A Case of Systemic Capillary Leak Syndrome with Severe Cardiac Dysfunction after mRNA Vaccination for COVID-19

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Short title

SCLS after COVID-19 mRNA Vaccine

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Brief summary

Cardiogenic shock with systolic dysfunction and global myocardial edema requiring venoarterial extracorporeal membrane oxygenation and Impella was observed in a patient after COVID-19 mRNA vaccination (BNT162b2). Based on findings such as hemoconcentration, hypoalbuminemia, and no obvious inflammatory cell infiltration on myocardial biopsy, we diagnosed systemic capillary leak syndrome, and pulsed steroid therapy resulted in rapid improvement in cardiac function.

Abstract

A 53-year-old woman with no significant medical history developed cardiogenic shock four days after receiving the second dose of the COVID-19 mRNA vaccine (BNT162b2, Pfizer/BioNtech). The patient required extracorporeal membrane oxygenation and an Impella device. Based on significant hemoconcentration, decreased plasma protein levels, and pathological findings in myocardial specimens, the patient was diagnosed with vaccination-induced fulminant systemic capillary leak syndrome (SCLS) with severe cardiac dysfunction. This case highlights that SCLS can occur after COVID-19 mRNA vaccination and may be associated with cardiac dysfunction. In patients with cardiogenic shock, hemoconcentration, and hypoalbuminemia after vaccination, SCLS should be considered.

Manuscript text

Case

A 53-year-old woman received the second dose of the COVID-19 mRNA vaccine (BNT162b2, Pfizer/BioNTech) four days prior to admission. Fever occurred on the day after the vaccination and resolved two days later. However, general malaise and loss of appetite worsened, requiring transportation to the emergency department of the initial hospital. On admission to the initial hospital, there were no other symptoms, such as hives, flushing and conjunctival swelling to suggest anaphylaxis. Systolic blood pressure was 66 mmHg and heart rate was 139 beats/min. Hemoglobin, Troponin-T, and BNP levels were remarkably elevated (20.8 g/dL, 7.6 ng/mL, 1676 pg/mL, respectively). Left ventricular ejection fraction (LVEF) was significantly reduced to 17% with severe myocardial edema noted on echocardiogram. After infusion of noradrenaline (0.3 mcg/kg/h) and dobutamine (1.8 mcg/kg/h), an emergency coronary angiography revealed no coronary artery stenosis and fulminant myocarditis (FM) was suspected. Intubation was achieved relatively easily with no oral/buccal edema noted and after insertion of extracorporeal membrane oxygenation (ECMO) and an intra-aortic balloon pumping (IABP), the patient was transferred to our hospital. At the time of admission to our hospital, the peripheral extremities were cold, and systemic computed tomography showed no abnormalities other than whole-body edema,

pericardial effusion, and a small amount of bilateral pleural effusion. Electrocardiography revealed low voltage and no ST-segment elevation (Figure 1). Echocardiography showed diffuse severe hypokinesia and marked edema of the left and right ventricular myocardium. (interventricular septum thickness: 12.0 mm, posterior left ventricular wall thickness: 17.2 mm). Furthermore, no opening of the aortic valve was observed, which was caused by the afterload due to ECMO retrograde blood flow (Video 1). The IABP was replaced with an Impella CP device to prevent left ventricular thrombosis and reduce the left ventricular end-diastolic pressure. At the time of the Impella CP insertion, the activated partial thromboplastin time (aPTT) was significantly prolonged, reflecting coagulation abnormalities despite not receiving heparin since arrival. Three myocardial biopsies from the right ventricular septum were performed to differentiate myocarditis. Hematoxylin and eosin staining of the myocardial tissues revealed no inflammatory cell infiltration and limited injuries within the myocardium. Immunostaining also detected no immuno-positive cells (Figure 2). A significant decrease in plasma proteins was detected, including albumin (0.8 g/dL), complement (C3: 12.2 mg/dL, C4: 4.5 mg/dL), γ-globulin (IgG: 184 mg/dL, IgA: 28 mg/dL, IgM: 30 mg/dL), and coagulation factors (prothrombin time-international normalized ratio: 1.75, antithrombin-III (AT-Ⅲ): 26.0%, fibrinogen: 102 mg/dL), which reflected an increase in vascular permeability. Additionally, the blood pressure could not be maintained without a large dose of noradrenaline even with

sufficient ECMO flow, making us suspect a significantly decreased vascular resistance. We diagnosed the patients with SCLS with severe cardiac dysfunction based on decreased blood pressure, low albumin, and hemoconcentration without inflammatory findings in myocardial pathology.

Intravenous corticosteroids (methylprednisolone 500 mg twice a day) were administered for three days to improve vascular hyperpermeability and vascular resistance, in addition to vasopressin for maintaining blood pressure. From the next day, cardiac function improved rapidly, and catecholamine and vasopressin were gradually reduced. On the fourth day, ECMO was removed, and the Impella CP was removed on the following day. Blood, sputum, and urine cultures of samples collected at admission, and various polymerase chain reaction tests for viruses in the myocardium were all negative. Magnetic resonance imaging showed no evidence of late gadolinium enhancement. Although the patient's weight had increased by approximately 15 kg from baseline, it was rapidly improved by diuretics.

After progressive reduction in dosage, corticosteroids were discontinued on the 23rd day without re-exacerbation of cardiac dysfunction or altered hemodynamics. The LVEF improved to 68%, although some pericardial effusion persisted (Video 2).

Discussion

Although there have been several reports of FM after COVID-19 vaccination,[1] to the best of our knowledge, this is the first report of SCLS with severe cardiac dysfunction requiring mechanical circulatory support after COVID-19 mRNA vaccination.

SCLS is a rare disorder that can lead to multiple organ failure due to rapid extravasation of body fluids and plasma proteins owing to a potentially life-threatening transient hyperpermeability of the vascular endothelium. It is characterized by episodes of severe hypotension, hypoalbuminemia, hemoconcentration, and systemic edema.[2] Previously, Juthier et al. reported a case in which myocardial injury was caused by excessive interstitial edema, as in our case. [3]

Although it is difficult to make a strict distinction between FM and SCLS, we finally diagnosed SCLS with severe cardiac dysfunction based on our findings of hemoconcentration and a marked reduction in plasma proteins. SCLS has been reported after receiving adenovirus vector (ChAdOx1 nCOV-19, Ad26.COV2.S) and mRNA (mRNA-1273, BNT162b2) vaccines against COVID-19. Although only one case of SCLS per 13 million ChAdOx1 nCOV-19 vaccine doses has been reported in Europe, the precise number of cases requiring mechanical circulatory support is unclear.[4-6] SCLS is reported to be caused by drugs such as human recombinant interleukin-2 (IL-2) and interferons, hematological malignancies, infectious diseases such as COVID-19 and influenza, and autoimmune diseases. Up to 79% of adult patients with SCLS have monoclonal gammopathy of undetermined significance (especially IgG kappa); however,

such involvement was not detected in this case. The mortality rate of SCLS is 20–30%, and treatment includes steroids and high-dose intravenous immunoglobulins.[2] The exact etiology of vaccine-associated SCLS remains unknown. After vaccination, a strong response of CD8+ and CD4+ T cells and production of interferon γ and IL-2 have been observed, and an association between IL-2 and SCLS has been reported.[7] Thus, immune response to the vaccination may be involved in SCLS; however, further research is needed to verify the cause.

In our patient, significant prolongation of aPTT and reduction of plasma proteins, including coagulation factors such as AT-III and fibrinogen, were observed at the time of admission. Although the cross-mixing test was not performed, all plasma protein levels normalized after recovery. Thus, we hypothesized that these issues were caused by the leakage of coagulation factors rather than production of autoantibodies. Multiglandular hormone deficiency has been reported in a patient with SCLS.[8] Although thyroid and adrenal hormone levels were normal after improvement of cardiac function in our patient, multiglandular hormones might have been deficient due to extravasation. Therefore, in addition to suppressing the immune response described above, prompt pulsed steroid therapy might have been effective against adrenal insufficiency caused by extravasated proteins.

Even if there are no abnormalities such as anaphylaxis immediately after vaccination, attention should be paid to serious complications such as myocarditis and SCLS during the initial days after vaccination.

Conclusion

FM-like hemodynamics can be caused by SCLS after COVID-19 mRNA vaccination.

Novel teaching point

In patients with cardiogenic shock after COVID-19 vaccination, SCLS with cardiac dysfunction, as well as, FM should be considered.

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Disclosures

None.

References

1. Abbate A, Gavin J, Madanchi N, et al. Fulminant myocarditis and systemic hyperinflammation temporally associated with BNT162b2 mRNA COVID-19 vaccination in two patients. Int J Cardiol 2021;340:119-21.

2. Bichon A, Bourenne J, Gainnier M, Carvelli J. Capillary leak syndrome: state of the art in 2021. Rev Med Interne 2021;42:789-96.

3. Juthier F, Ennezat PV, Fornes P, et al. Myocardial involvement in systemic capillary leak syndrome: first demonstration by pathologic findings. Eur Heart J Acute Cardiovasc Care 2012;1:248-52.

4. Robichaud J, Côté C, Côté F. Systemic capillary leak syndrome after ChAdOx1 nCOV-19 (Oxford-AstraZeneca) vaccination. CMAJ 2021;193:E1341-E1344.

5. Choi GJ, Baek SH, Kim J, et al. Fatal systemic capillary leak syndrome after SARS-COV-2vaccination in patient with multiple myeloma. Emerg Infect Dis 2021;27. doi: 10.3201/eid2711.211723. Online ahead of print.

6. Matheny M, Maleque N, Channell N, et al. Severe exacerbations of systemic capillary leak syndrome after COVID-19 vaccination: a case series. Ann Intern Med 2021;174:1476-8.

7. Sahin U, Muik A, Vogler I, et al. BNT162b2 vaccine induces neutralizing antibodies and poly-specific T cells in humans. Nature 2021;595:572-7.

8. Then C, Ritzel K, Seibold C, Mann JFE, Reincke M. Multiglandular hormone deficiency in a patient with systemic capillary leak syndrome. Case Rep Med 2015;2015:958283.

Figure legends

Figure 1. Electrocardiogram on admission

An electrocardiogram obtained after admission to our hospital revealed sinus rhythm with low voltage and no ST-segment elevation.

Figure 2. Staining of myocardial tissue

Hematoxylin and eosin staining of the myocardial tissue revealed no inflammatory cell infiltrates, eosinophils, and multinucleated giant cells, but showed limited injuries within the myocardium. Immunostaining also revealed CD3-negative, CD4-negative, CD8-negative, CD20-negative, CD68-negative.

Video legends:

Video 1. Echocardiogram on admission (A: long-axis view, B: short-axis view)

The echocardiogram shows no opening of the aortic valve. Left ventricular ejection fraction (LVEF) was 10% with pericardial effusion. Interventricular septum thickness/posterior left ventricular wall thickness (IVST/PWT): 12.0/17.2 mm

Video 2. Echocardiogram on the 23rd day (A: long-axis view, B: short-axis view)

Left ventricular ejection fraction (LVEF) improved to 68%, although some pericardial effusion remained. Interventricular septum thickness/posterior left ventricular wall thickness (IVST/PWT): 8.3/10.5 mm

Figure 1

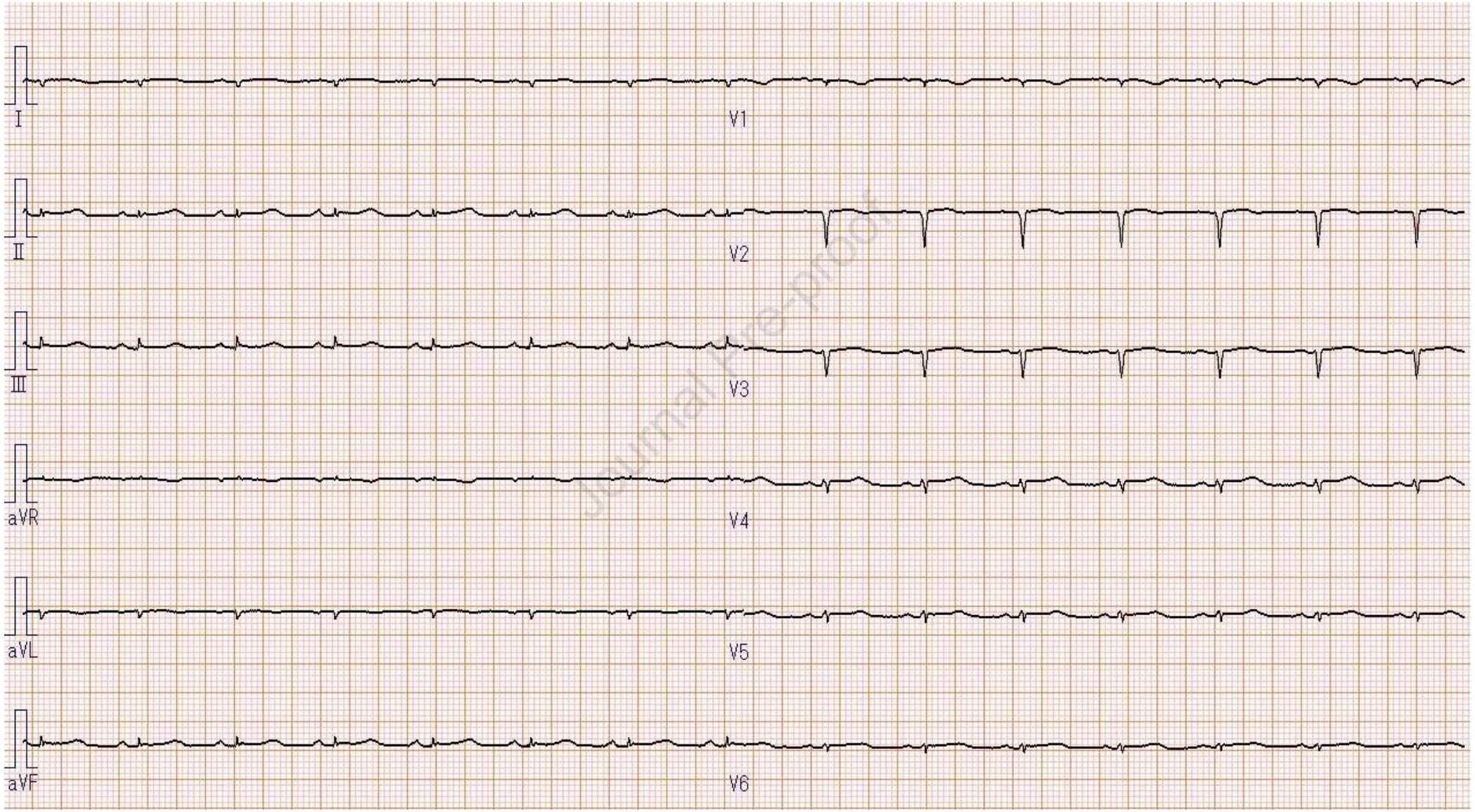

Figure 2